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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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ART UNIT	**PAPER NUMBER**
1642	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/724,000	Applicant(s) POLVERINO ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *1-8,10-12,18-36,43-45 and 48-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,13-17,37-42,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-56* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5 and 9*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-56 are pending in the application.

2. The amendment filed on November 28, 2000 in Paper No. 6 is acknowledged and has been entered.

3. The election with traverse of Group 4 filed on May 24, 2001 in Paper No. 8 is acknowledged and has been entered. However, with regard to Paper No. 8, the Applicant mistakenly indicated that the Group 4 comprises claims 40-45, 49, and 50, claims that were not restricted to the elected group in the previous Office Action mailed on April 27, 2001 (Paper No. 7). For clarification, Group 4 consists of claims 9, 13-17, 37-42, 46, and 47. Therefore, claims 1-8, 10-12, 18-36, 43-45, and 48-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 9, 13-17, 37-42, 46, and 47 are currently under prosecution.

Election/Restrictions

5. Applicant's election with traverse of Group 4 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that searching Groups 3 and 4 would not constitute a serious burden. This is not found persuasive because the search required for examination of Group 3 is not coextensive with the search required for examination of Group 4. Different searches are required for each group and different issues pertaining to the patentability of each group must be considered.

The requirement is still deemed proper and is therefore made FINAL.

Oath/Declaration

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The application is a continuation-in-part of US Application Serial No. 09/599,087 filed on June 21, 2000. The declaration is defective because the claim for benefit of the earlier filing date of the parent application is entered under the form paragraph that claims benefit under 35 USC § 119. Therefore, the declaration does not state that the application claims domestic priority under 35 USC § 120. Furthermore, the declaration does not state that the person making the declaration in this continuation-in-part application filed under the conditions specified in 35 USC § 120, which discloses and claims subject matter in addition to that disclosed in the prior co-pending application, acknowledges the duty to disclose to the Office all information known to the person to be material to patentability as defined in 37 CFR 1.56 that occurred between the filing date of the prior application and the national filing date of the continuation-in-part application.

Claim Objections

7. Claim 39 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 39 is drawn to the composition of claim 37 wherein the polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 6. SEQ ID NO: 6 is a fragment of the amino acid sequence set forth in SEQ ID NO: 5. Claims 13, 14, or 15, from which claim 37 depends, are drawn to a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5 or a fragment thereof. Therefore, because claim 39 only requires that the polypeptide include the amino acid sequence set forth in SEQ ID NO: 6, claim 39 does not further limit the subject matter of claim 37, which requires that the polypeptide include the amino acid sequence set forth in SEQ ID NO: 5 or a

fragment thereof and therefore also include the amino acid sequence set forth in SEQ ID NO: 6, which is a fragment of SEQ ID NO: 5.

8. Claims 9, 13-17, 37-42, 46, and 47 are objected to because of the following informalities: The claims are drawn in the alternative to a non-elected invention(s). Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 9, 14-17, 37-42, 46, and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 5 or a fragment thereof, does not reasonably provide enablement for an isolated polypeptide comprising an amino acid sequence that is at least about 70% identical to the amino acid sequence set forth in SEQ ID NO: 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to an isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5 or a fragment thereof. The claims are also drawn to an isolated polypeptide or a fragment thereof comprising an amino acid sequence that is at least about 70% identical to the amino acid sequence set forth in SEQ ID NO: 5. The claims also encompass a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5 wherein at least one modification has been made, including deletions, insertions, substitutions, and truncations. Therefore, even though the claims recite the limitation that the polypeptide have an activity of the polypeptide that consists of the amino acid sequence set forth in SEQ ID NO: 5, the claims read on any

polypeptide, because any polypeptide will have an activity of the polypeptide that consists of the amino acid sequence set forth in SEQ ID NO: 5. For example, any polypeptide will have antigenic activity and most, if not all polypeptides will be active substrates for a protease. Consequently, given the broadest reasonable interpretation, the claims encompass any and all isolated polypeptides.

The specification teaches the amino acid sequence of a human protein, designated Secs-1, which consists of the amino acid sequence set forth in SEQ ID NO: 5 (pages 85-87 and Figures 1-4). The specification teaches that the gene encoding Secs-1 is expressed in some, but not all cancer cell lines (pages 91-92 and Figures 5-7). However, the specification also teaches that the gene is expressed at high levels in normal epithelial cells. In examples 1-5, respectively, the specification teaches methods for cloning the gene encoding Secs-1, methods for analyzing the expression of the gene encoding Secs-1, methods for producing the Secs-1 polypeptide, and methods for producing a transgenic mouse expressing human Secs-1 (pages 85-96). Finally, in the remaining examples, the specification discloses conventional methods that might be used to characterize the biological activity of Secs-1 (pages 96-98).

The teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims. The reason for this conclusion is set forth below:

As noted above, the breadth of the claims actually encompasses any and all polypeptides. Clearly the teachings of the specification cannot be extrapolated to the enablement of claims with such breadth. More narrowly interpreted, the claims encompass variants of the Secs-1 polypeptide, which differ in amino acid sequence from the polypeptide sequence of SEQ ID NO: 5. For example, the claims encompass polypeptides that are only about 70% identical to SEQ ID NO: 5. These polypeptides will necessarily differ from SEQ ID NO: 5 in amino acid sequence at about 30 out of every 70 positions. Also, the claims also encompass polypeptides comprising only fragments of the amino acid sequence set forth in SEQ ID NO: 5. On the other hand, it is noted that polypeptides with relatively more moderate variations in the amino acid of SEQ ID NO: 5 are encompassed by the claims. For example, claim 15 encompasses a

polypeptide that differs from SEQ ID NO: 5 at only one position by the conservative substitution of one amino acid for another that has similar chemical properties as the one being replaced.

The skilled artisan cannot accurately predict the inherent effects of dissimilarity in the amino acid sequences of polypeptides upon protein structure and function. Bowie, et al (*Science* **257**: 1306-1310, 1990) teach that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Bowie, et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2).

Burgess, et al (*Journal of Cell Biology* **111**: 2129-2138, 1990) exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. This reference teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. As another example of the unpredictability in the art, Lazar et al (*Molecular and Cellular Biology*, 1988, **8**: 1247-1252) teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. For emphasis, it is noted that Lazar, et al teaches that the conservative substitution of aspartic acid for glutamic acid causes a substantial loss of the protein's activity.

The physiologic activity of the Secs-1 polypeptide is not disclosed in the specification. Moreover, the specification does not specifically identify an activity of the

Secs-1 polypeptide; so apart from teaching methods for determining the activities that are obviously characteristic of all polypeptides (e.g., antigenicity), the specification does not enable the use of the Secs-1 polypeptide, *per se*.

Considering the teachings of the references cited above, it is apparent that even a single amino acid substitution could often dramatically affect the biological activity and the structure-function characteristics of a protein. Therefore, it is clear that one skilled in the art cannot immediately conclude that any of the claimed variants of the Secs-1 polypeptide will have an activity, including antigenicity that is identical or even similar to the Secs-1 polypeptide. The specification does not teach how the claimed variants of the Secs-1 polypeptide can be used. Based upon the teachings of Bowie, et al, Burgess, et al, and Lazar, et al, it is especially clear that one skilled in the art cannot predict whether the broadly claimed proteins that have an amino acid sequence that is less than 100% identical to SEQ ID NO: 5 will function or can be used in accordance with the disclosed utilities in the specification.

In view of the above, it is apparent that one skilled in the art cannot practice the claimed invention with a reasonable expectation of success without first embarking upon a course of extensive and therefore undue experimentation. Therefore, the specification fails to meet the requirements of 35 USC § 112, first paragraph as it does not enable any person skilled in the art to which it pertains to make and/or use the invention commensurate in scope with the claims.

11. Claims 37-42, 46, and 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a pharmaceutical composition comprising a polypeptide or a fragment thereof, which comprises an amino acid sequence that is at least about 70% identical to the amino acid sequence set forth in SEQ ID NO: 5. While claims 40-42, 46, and 47 are specifically drawn to a derivatized or fusion polypeptide, which comprises an amino acid sequence or a fragment thereof that is at least about 70%

identical to the amino acid sequence set forth in SEQ ID NO: 5, the specification teaches that the derivatized or fusion polypeptides are to be used to therapeutically. These claims are, therefore, encompassed by the claims drawn to a pharmaceutical composition comprising a polypeptide or a fragment thereof, which comprises an amino acid sequence that is at least about 70% identical to the amino acid sequence set forth in SEQ ID NO: 5. Support for this conclusion is found in the specification, for example, on page 27, and particularly in Table II (page 27), wherein Applicant discloses that fusion polypeptides comprising a portion of an immunoglobulin molecule are used therapeutically. Also, on page 57, lines 7-12, the specification discloses that derivatives of the claimed polypeptide can be administered therapeutically.

The specification teaches that which is set forth in the 35 USC § 112, first paragraph rejection above. The specification also teaches conventional wisdom regarding the production and use of pharmaceutical compositions comprising therapeutically active polypeptides (pages 63-69) and the specification discloses potential therapeutic uses for the claimed pharmaceutical compositions on pages 80-83.

The teachings of the specification, however, cannot be extrapolated to the enablement of the invention commensurate in scope with the claims. The reason for this conclusion is that there is insufficient guidance and exemplification in the specification that would serve to enable one skilled in the art to make and/or use the invention with a reasonable expectation of success. Furthermore, in the absence of exemplification and based only upon the teachings of the specification, one skilled in the art cannot predict whether the claimed invention can be made and used effectively to prevent, treat, or diagnose a disease or any other abnormal physiologic condition. Therefore, the skilled artisan would have to first perform extensive experimentation in order to determine whether the claimed invention can be made and used effectively.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). The factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the

art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

It is well known that the art of drug discovery is highly unpredictable. For example, Gura (*Science* **278**: 1041-1042, 1997) teaches that researchers face the problem of sifting through potential therapeutic agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs).

Clearly one skilled in the art cannot predict whether a pharmaceutical composition comprising the human Secs-1 polypeptide can be used therapeutically. Of course, for that matter, one skilled in the art cannot predict whether a pharmaceutical agent comprising a variant, homolog, ortholog, fragment, derivative, or fusion of the Secs-1 polypeptide can be used therapeutically, since any modification may alter the activity of Secs-1. The teachings of Burgess, et al (cited supra) and Lazar, et al (cited supra), which were referenced in the 35 USC§ 112, first paragraph rejection above provide evidence of this latter fact. Consequently, the effects of putative pharmaceutical agents, such as the Secs-1 polypeptide or derivatives and variants thereof, can only be determined empirically. Even in the presence of scientific data suggesting that a pharmaceutical agent can be used efficaciously, there is need for caution. The effects of a pharmaceutical agent upon a culture of cells or an experimental animal may be entirely different from the effects of the agent upon a human patient. For example, Bergers, et al (*Current Opinion in Genetics and Development* **10**: 120-127, 2000) disclose that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers, et al comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, columns 1-2). Thus, it is relatively clear that one skilled in the art cannot predict the effect of administering a pharmaceutical agent that comprises the Secs-1 polypeptide or a

derivative or fragment thereof to a subject in need of therapy. Rather than ameliorating the disease, it is quite possible, in light of the teachings of Bergers, et al, that the agent may promote the progression of the disease.

Nevertheless, the specification does not specifically teach how the claimed pharmaceutical compositions are to be used. Moreover, the specification does not specifically teach which diseases or abnormal physiologic conditions can be prevented, treated, or diagnosed using the claimed pharmaceutical compositions. In fact, in the absence of sufficient information regarding the activity of the Secs-1 polypeptide it is difficult to even imagine which diseases might be treated or diagnosed using the invention. Actually, the specification is entirely deficient in teaching an association between the Secs-1 polypeptide and the etiology or pathogenesis of any one disease. There may be no such association, in which case, while the specification is clearly not enabling, the invention may not have utility. Based only upon the disclosure, certainly one skilled in the relevant art cannot predict whether the Secs-1 polypeptide is involved in the etiology or pathology of a specific disease. De Plaen, et al (*Immunogenetics* **40**: 360-369, 1994) review the expression of twelve genes of the MAGE family. De Plaen, et al teach that six of the members of the gene family are expressed at a high level in a number of tumors of various histological types and five were very weakly expressed in all samples tested, but one, MAGE 7, was not transcribed at all in the ninety-five tumor samples tested (see page 367, column 1). Obviously, therefore, not all MAGE family proteins are associated with tumors and it is not apparent what, if any, association the weakly expressed MAGE proteins have with tumors. Accordingly, in light of the teachings of De Plaen, et al, it is clear that one skilled in the relevant art would not conclude that a given protein is associated with neoplastic disease despite the fact that related family members might be. Therefore, for the reason set forth in this example, one skilled in the relevant art cannot predict, based upon the information disclosed in the specification, that the Secs-1 polypeptide has any association with the etiology or pathology of cancer or any other abnormal condition.

It is important to note that the actual biologic activity of Secs-1 polypeptide is not disclosed in the specification. Nevertheless, even if it were so that the activity of Secs-1

polypeptide was reasonably defined, many polypeptides are known to have entirely different effects upon different cell types. For example, Baxter, et al (*Journal of Biological Chemistry* **274**: 9539-9547, 1999) teaches that the activity of TNF-α is ambiguous since it can induce a cell to proliferate or it can have quite the opposite effect, causing a cell to undergo programmed cell death (i.e., apoptosis). Thus, it is reasonably clear that the skilled artisan cannot practice the claimed invention with a reasonable expectation of success, because the specification fails to demonstrate that the pharmaceutical composition can be used effectively to treat any one disease or abnormal condition. Certainly, in view of the teachings of Baxter, et al, one skilled in the art cannot predict whether the invention can be used effectively and would therefore be forced to perform undue experimentation in order to practice the invention.

Finally, it is noted that in at least one embodiment the claimed pharmaceutical composition can comprise an adjuvant, which suggests that Applicants intend the invention to be used as a vaccine to stimulate an immune response directed against cells that express Secs-1. With regard to vaccines, *per se*, considerable limitations are known in the art, which substantially limit the efficacy of such therapeutic approaches. Bodey, et al (*Anticancer Research* **20**: 2665-2676, 2000) teach that "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2) and "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). In the abstract Bodey, et al disclose:

> Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

Clearly, if a tumor does not express the antigen that is specifically bound by the antibody the use of a pharmaceutical composition comprising that antibody will not be effective. However, as Bodey, et al teach, use of such a pharmaceutical composition may only serve to select against tumor cells that express the antigen, while promoting the growth of tumor cells that do not express the antigen. Furthermore, since normal epithelial cells express Secs-1 polypeptide, as the specification teaches, it is not clear that immune cells stimulated by the claimed pharmaceutical composition can selectively target diseased cells. Thus, while the efficacy of the claimed pharmaceutical composition cannot be predicted or determined without undue experimentation, clearly one skilled in the art would have reason to doubt that the pharmaceutical composition can be used effectively.

In addition to vaccines, the claims also encompass a variety of other types of pharmaceutical compositions that might be used in different therapeutic strategies. However, as with vaccines, there is absolutely no factual evidence that these pharmaceutical compositions can be used effectively. Moreover, most, if not all of these therapeutic strategies are known to be subject to significant limitations.

With regard to cancer therapy, undue experimentation would be required to determine how much or how often antibody must be delivered to a human or any other subject to effect a suitable level of tumor growth inhibition, and whether or not such dosages are tolerable to patients, without causing non-specific toxicity. Because there are no working examples (or for that matter, prophetic examples) which demonstrate (or anticipate) that the claimed pharmaceutical composition can be used to effectively, in view of the high level of unpredictability in the art, one skilled in the art cannot predict the efficacy of the invention or, in other words, whether the invention can be used clinically. Therefore, one skilled in the art cannot practice the invention commensurate in scope with the claims with a reasonable expectation of success without being forced to perform undue experimentation.

With particular regard to the treatment of patients diagnosed with cancer, the refractory nature of diseased cells to drugs is well known in the art. Jain (*Scientific American* **271**: 58-65, 1994) teaches that scientists need to put expanded effort into

uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (page 65, column 3). Curti (*Critical Reviews in Oncology/Hematology* **14**: 29-39, 1993) teaches that tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited. Curti also teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and, if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (paragraph bridging pages 29-30). Curti concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (page 36, column 2). Thus, it is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that a pharmaceutical agent comprising the Secs-1 polypeptide can be used to effectively treat a subject diagnosed with cancer or any other disease, based only upon the demonstration that Secs-1 is expressed some cancer cell lines, in addition to normal epithelial cells.

In addition, it is well known that anti-tumor agents must accomplish several tasks to be effective. The agents must be delivered into the circulation and interact at the proper site, and they must do so at a sufficient concentration and for a sufficient period of time so as to be effective. Also, the targeted cells must not have an alternate means of survival despite action at the proper site for the drug. In addition, variables such as biological stability, half-life, and clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation, or due to an inherently short half-life. The composition may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted. Alternatively, the composition may be absorbed by fluids, cells and tissues where the formulation has no effect and circulation into the target area may be insufficient to carry the composition and to permit a large enough local concentration to be established. However, the specification provides insufficient guidance with regard to these issues to

enable the skilled artisan to practice the invention with a reasonable expectation of success without first performing extensive and undue experimentation.

In summary, in the absence of exemplification and sufficient guidance, the specification clearly fails to meet the enablement requirements of 35 USC § 112, first paragraph. Given only the teachings of the specification, because of the high degree of unpredictability in the art, the skilled artisan cannot make and/or use the invention with a reasonable expectation of success. Accordingly, one skilled in the art would be forced to perform extensive and undue experimentation in order to practice the invention successfully.

12. Claims 9, 14-17, 37-42, 46, and 47 also are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description sets forth SEQ ID NO: 5, which is the amino acid sequence of the human polypeptide designated Secs-1. The written description also set forth in SEQ ID NO: 2 the amino acid sequence of an ortholog of the human Secs-1 polypeptide, namely the amino acid sequence of the mouse Secs-1 (or muSmac2) polypeptide.

The claims, however, encompass a broad genus of polypeptides having at least 70% identity to the amino acid sequence set forth in SEQ ID NO: 5. For example, the claims encompass naturally occurring variants of Secs-1 that would be encoded by different alleles of the gene encoding Secs-1 or possibly by alternatively spliced messenger RNA molecules. In fact, claim 14 is specifically recites a limitation that the claimed polypeptide comprise an amino acid sequence for an allelic variant or splice variant of the amino acid sequence of SEQ ID NO: 5.

The disclosure of two species of the claimed genus of polypeptides, namely SEQ ID NO: 2 and 5 is considered insufficient to meet the written description requirement of 35 USC § 112, first paragraph for the following reason:

The structures and amino acid sequences of the vast majority of these congeneric species of polypeptides are not disclosed in the specification. More particularly, the structures and amino acid sequences of the claimed polypeptides that comprise the amino acid sequence of an allelic variant or splice variant of the amino acid sequence of SEQ ID NO: 5 are not disclosed. In accordance, the claimed subject matter is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (page 115).

Although drawn to the nucleic acid art the findings of *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016 are clearly relevant to the instant invention. *Fiers v. Revel* and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.* found that adequate written description requires more than a mere statement that it (a nucleic acid) is part of the invention. The nucleic acid itself is required; or by inference, in the instant case, the claimed amino acid sequence of an allelic variant or splice variant of the amino acid sequence of SEQ ID NO: 5 itself is required.

Furthermore, in *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written

description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA [molecule] 'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Although these court findings are drawn to the DNA art, the findings are clearly applicable to the claimed naturally occurring amino acid sequences. The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. In fact, as set forth in the 35 USC § 112, first rejection above, the specification does not include a description of the physiologic activity of the Secs-1 polypeptide. Furthermore, there is no description of the sites at which variability may be tolerated and there is no information regarding the relation of the polypeptide's structure to its function. The prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed by the claims. Therefore, because the amino acid sequences of the claimed genus of polypeptides are not disclosed and because no identifying characteristic or property is provided, one skilled in the art cannot reasonably identify those polypeptides that are encompassed by the claims. In other words, the specification fails to describe the common attributes or characteristics that identify members of the genus and for this reason, the disclosure is considered to be inadequate to meet the written description requirements of 35 USC § 112, first paragraph.

Additionally, the absence of sufficient disclosure to meet the written description requirement of 35 USC § 112, first paragraph suggests that Applicant did not have possession of the invention at the time the application was filed. Furthermore, Applicant is reminded that conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method for isolating and characterizing

a polypeptide. It is equally, if not more apparent that Applicant was not in possession of the claimed pharmaceutical compositions, the claimed polypeptide derivatives, or the claimed fusion polypeptides at the time the application was filed. There is simply no factual evidence of record that would serve to convince the skilled artisan that Applicant had possession of the invention at the time the application was filed.

In summary, adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method for isolating the gene or messenger RNA encoding the allelic or splice variants of SEQ ID NO: 5. The polypeptide sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. With the exception of SEQ ID NO: 5, the skilled artisan cannot immediately envision the detailed structure of the encompassed naturally occurring amino acid sequences. Consequently, the disclosure is insufficient to meet the written description requirement of 35 USC 112, first paragraph and to support the generic claims in accordance with *The Guidelines for Examination of Patent Applications* (66 FR 1099-1111, 5 January 2001).

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 9, 13, 16, 17, 37-42, 46, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9, 14-17, 37-42, 46, and 47 are vague and indefinite because claims 2, 3, and 14-16 recite the phrase "has an activity". The use of the phrase renders the claims vague and indefinite because it is unclear to which activity the claim refers and therefore it is unclear how one of ordinary skill in the art can determine the activity to which the claim refers. Furthermore, the claims are so broad as to be vague. Accordingly one of

ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention.

Claims 9, 13, 16, 37-42, 46, and 47 are indefinite because claims 1, 2, and 3, from which claim 9 depends, and claim 13 recite the phrase "the DNA insert in ATCC Deposit Nos. PTA-1753". The use of the phrase renders the claims indefinite because it is not clear to which DNA insert the claim refers. Accordingly, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention. Amending one or more independent claims of the elected invention to recite, for example, the phrase "wherein said insert comprises a polynucleotide sequence that encodes the amino acid sequence set forth in SEQ ID NO: 5" can obviate this rejection.

Claims 9 and 16 are also indefinite because claim 1, from which claims 9 and 16 depend, recites the phrase "hybridizes under moderately or highly stringent conditions". Moderately and highly stringent conditions are not specifically defined in the claim. Therefore, the claim encompasses conditions that range in stringency from very permissive to very selective and the specification does not provide a standard for ascertaining the requisite degree of stringency. Furthermore, it is unclear whether the claim requires the nucleotide sequence to hybridize specifically and selectively to the complement of (a) – (c) or merely hybridize non-specifically or non-selectively. Consequently, one of ordinary skill in the art is not be reasonably apprised of the metes and bounds of the invention. Amending claim 1 to recite the specific conditions and to recite, for example, the phrase "a nucleotide sequence that specifically and selectively hybridizes under [specific conditions]" can obviate this rejection.

Where a trademark or trade name is used in a claim, MPEP 7.35.01 reads, "the claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material product. On the other hand, a trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name." See *Ex parte Simpson*, 218 USPQ 1020 (PTO Board of Patent Appeals and Interferences, 1982). Therefore, in the instant case, claim 17 is indefinite because

of the use of the trademark name "BestFit™" to identify a fixative. Amending the claims to delete the trademark name "BestFit™" can obviate these rejections.

Claim 17 is also indefinite in the use of the terms "GAP", "BLASTP", "FASTA", "BLASTA", "BLASTX", "BestFix™", and the "Smith-Waterman" algorithm. These terms identify algorithms, which are subject to change, and are implemented by software programs that are further subject to change, thereby creating different versions. Accordingly, the result acquired when using the software programs that implement these algorithms might also change. Therefore, it is necessary to identify the algorithm and software by the version and the date of the version, so that one of ordinary skill in the art is reasonably apprised of the metes and bounds of the invention.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 9, 13, 14, 16, and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by The FAPESP/LICR Human Cancer Genome Project (GenBank EST Database Accession No. AW351839, 1999), as evidenced by a USPTO database search using SEQ ID NO: 5 as a query (see USPTO Search Report US-09-599-087-5.rst, result 1).

The FAPESP/LICR Human Cancer Genome Project teach the amino acid sequence of a polypeptide that is at least about 70% identical to the amino acid sequence set forth in SEQ ID NO: 5. In fact, the amino acid sequence of the

polypeptide that is 100% identical to the amino acid sequence set forth in SEQ ID NO: 5.

Because the polypeptide of the prior art has the same amino acid sequence as the claimed polypeptide, the polypeptide of the prior art will have an activity of the polypeptide of SEQ ID NO: 5. This is an inherent property of the prior art polypeptide. Furthermore, the search engine used to determine the percent identity uses the Smith-Waterman algorithm.

All the limitations of the claims are met.

17. Claims 9 and 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillier, et al (GenBank EST Database Accession No. AA422178, 1997), as evidenced by a USPTO database search using SEQ ID NO: 5 as a query (see USPTO Search Report US-09-599-087-5.rst, result 2).

Hillier, et al teach the amino acid sequence of a polypeptide that is at least about 70% identical to the amino acid sequence set forth in SEQ ID NO: 5. In fact, the amino acid sequence of the polypeptide that is 100% identical to the amino acid sequence set forth in SEQ ID NO: 5 over the region spanning from the amino acid at position 1 to the amino acid at position 76. Therefore, the polypeptide of Hillier, et al is truncated at the C-terminus, encoding a fragment of SEQ ID NO: 5 comprising at least about 25 amino acid residues.

Because the polypeptide of the prior art has the same amino acid sequence as the claimed polypeptide, the polypeptide of the prior art will have an activity of the polypeptide of SEQ ID NO: 5. This is an inherent property of the prior art polypeptide. Furthermore, search engine used to determine the percent identity was uses the Smith-Waterman algorithm.

All the limitations of the claims are met.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 9, 13, 14, 16, 17, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over The FAPESP/LICR Human Cancer Genome Project (GenBank EST Database Accession No. AW351839, 1999), as evidenced by a USPTO database search using SEQ ID NO: 5 as a query (see USPTO Search Report US-09-599-087-5.rst, result 1).

Refer to the corresponding 35 USC § 102(a) rejection above for an analysis of the claims.

The FAPESP/LICR Human Cancer Genome Project teach that which is set forth in the 35 USC § 102(a) rejection above. However, The FAPESP/LICR Human Cancer Genome Project do not disclose a fusion polypeptide comprising the polypeptide having the amino acid sequence set forth therein fused to a heterologous amino acid sequence.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the nucleic acid molecule of The FAPESP/LICR Human Cancer Genome Project so that the modified nucleic acid molecule would encode a fusion polypeptide comprising the polypeptide comprising the amino acid sequence of The FAPESP/LICR Human Cancer Genome Project fused to a FLAG-epitope tag, because the utility of FLAG-epitope tags in studies of a protein's activities is well established in the art. One of ordinary skill in the art at the time the invention was made would have been motivated to modify the nucleic acid molecule of The FAPESP/LICR Human Cancer Genome Project so that the modified nucleic acid molecule would encode a fusion polypeptide comprising the polypeptide comprising the amino acid sequence of The FAPESP/LICR Human Cancer Genome Project fused to a FLAG-epitope tag, because antibodies that specifically bind the epitope tag could be used to immunoprecipitate the fusion protein, facilitating purification and other studies.

20. Claims 9, 14-17, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillier, et al (GenBank EST Database Accession No. AA422178, 1997), as evidenced by a USPTO database search using SEQ ID NO: 5 as a query (see USPTO Search Report US-09-599-087-5.rst, result 2).

Refer to the corresponding 35 USC § 102(b) rejection above for an analysis of the claims.

Hillier, et al teach that which is set forth in the 35 USC § 102(b) rejection above. However, Hillier, et al do not disclose a fusion polypeptide comprising the polypeptide having the amino acid sequence set forth therein fused to a heterologous amino acid sequence.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the nucleic acid molecule of Hillier, et al so that the modified nucleic acid molecule would encode a fusion polypeptide comprising the polypeptide comprising the amino acid sequence of Hillier, et al fused to a FLAG-epitope tag, because the utility of FLAG-epitope tags in studies of a protein's activities is well established in the art. One of ordinary skill in the art at the time the invention was made would have been motivated to modify the nucleic acid molecule of Hillier, et al so that the modified nucleic acid molecule would encode a fusion polypeptide comprising the polypeptide comprising the amino acid sequence of Hillier, et al fused to a FLAG-epitope tag, because antibodies that specifically bind the epitope tag could be used to immunoprecipitate the fusion protein, facilitating purification and other studies.

Conclusion

21. No claims are allowed.

22. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Hillier, et al (GenBank EST Database Accession No. AA283751, 1997) teach a nucleic acid molecule that encodes a polypeptide that anticipates claims 9 and 14-17,

as evidenced by a USPTO database search using SEQ ID NO: 5 as a query (see USPTO Search Report US-09-599-087-5.rst, result 4).

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

DONNA WORTMAN
PRIMARY EXAMINER

slr
July 16, 2001